About Entrez

Text Version

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Browser
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
LinkOut
Cubby

Related Resources
Order Documents
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

Privacy Policy

- Search History will be lost after one hour of inactivity.
- To combine searches use # before search number, e.g., #2 AND #6.
- Search numbers may not be continuous; all searches are represented.

Search	Most Recent Queries	Time	Result
#8	**Related Articles** for **PubMed** (Select **10363974**)	09:17:14	143
#4	**Related Articles** for **PubMed** (Select **10632371**)	09:15:41	295
#5	Search Field: **All Fields,** Limits: **Publication Date from 1997 to 1998**	09:15:09	0
#3	Search **clinical cancer research[jour] AND 5[volume] AND 4279[page]** Field: **Title Word**	09:14:23	1
#2	Search **oncogene[jour] AND 55[volume] AND 587 [page]** Field: **Title Word**	09:06:57	0
#1	Search **oncogene[jour] AND 15[volume] AND 587 [page]** Field: **Title Word**	09:06:48	0

Clear History

☐ **1:** *190080 Links
V-MYC AVIAN MYELOCYTOMATOSIS VIRAL ONCOGENE HOMOLOG; MYC
Gene map locus 8q24.12-q24.13

☐ **2:** *600999 Links
MYC-ASSOCIATED ZINC FINGER PROTEIN; MAZ
Gene map locus 16p11.2

☐ **3:** *604899 Links
PREFOLDIN 5; PFDN5

☐ **4:** *602310 Links
RNA-BINDING MOTIF PROTEIN, SINGLE STRAND-INTERACTING, 1; RBMS1

☐ **5:** *603015 Links
TRANSFORMATION/TRANSCRIPTION DOMAIN-ASSOCIATED PROTEIN; TRRAP
Gene map locus 7q21.2-q22.1

☐ **6:** *173325 Links
JUNCTION PLAKOGLOBIN; JUP
Gene map locus 17q21

☐ **7:** *600382 Links
MYC PROMOTER-BINDING PROTEIN

☐ **8:** #150699 Links
LEIOMYOMA, UTERINE

☐ **9:** *113520 Links
BRANCHED-CHAIN AMINOTRANSFERASE 1; BCAT1
Gene map locus 12p12

☐ **10:** *604769 Links
PEROXIREDOXIN 3; PRDX3
Gene map locus 10q25-q26

☐ **11:** *602126 Links
ZINC FINGER PROTEIN 161, MOUSE, HOMOLOG OF; ZFP161
Gene map locus 18p11.21

☐ **12:** #502500 Links
ALZHEIMER DISEASE, SUSCEPTIBILITY TO, MITOCHONDRIAL

☐ **13:** *175100 Links
ADENOMATOUS POLYPOSIS OF THE COLON; APC
GARDNER SYNDROME, INCLUDED; GS, INCLUDED
Gene map locus 5q21-q22, 1p34.3-1p32.1

☐ **14:** *147582 Links
IRON-RESPONSIVE ELEMENT-BINDING PROTEIN 2; IREB2
Gene map locus Chr.15

☐ **15:** *134770 Links
FERRITIN HEAVY CHAIN 1; FTH1
IRON OVERLOAD, AUTOSOMAL DOMINANT, INCLUDED
Gene map locus 11q12-q13

☐ **16:** *123876 Links
CYSTEINE- AND GLYCINE-RICH PROTEIN 1; CSRP1
Gene map locus 1q32

☐ **17:** #113970 Links
BURKITT LYMPHOMA; BL
Gene map locus 8q24.12-q24.13

☐ **18:** *606535 Links
MYC-BINDING PROTEIN; MYCBP
Gene map locus 1p33-p32.2

☐ **19:** *606355 Links
DEAD/H BOX 18; DDX18

☐ **20:** *605277 Links
GLUCOCORTICOID RECEPTOR DNA-BINDING FACTOR 1; GRLF1
Gene map locus 19q13.2-q13.4

Display Titles Save Text Clip Add

Show: 20 Items 1-20 of 67 Page 1 of 4 Select page: **1 2 3 4**

*190080 Links

V-MYC AVIAN MYELOCYTOMATOSIS VIRAL ONCOGENE HOMOLOG; MYC

Alternative titles; symbols

ONCOGENE MYC
AVIAN MYELOCYTOMATOSIS VIRAL ONCOGENE HOMOLOG
PROTOONCOGENE HOMOLOGOUS TO MYELOCYTOMATOSIS VIRUS

Gene map locus 8q24.12-q24.13

TEXT

Sequences of the MYC oncogene have been highly conserved throughout evolution, from Drosophila to vertebrates (Shilo and Weinberg, 1981). Persson and Leder (1984) showed that the product of the MYC gene has a molecular weight of 65,000, is located predominantly in the nucleus, and binds to DNA.

Leder (1982) described in situ hybridization observations suggesting that the MYC locus is on chromosome 8 near 8q24, the breakpoint in Burkitt lymphoma translocations. Collins and Groudine (1982) found that the normal human homolog of the avian myc oncogene was present in multiple copies in the DNA of a malignant promyelocyte cell line derived from the peripheral blood of a patient with acute promyelocytic leukemia. Other human onc genes were not amplified. By the Southern blotting technique applied to somatic cell hybrids, Dalla-Favera et al. (1982) showed that the MYC gene is on chromosome 8. When hybrids between rodent cells and human Burkitt lymphoma cells were analyzed, they could show that the MYC gene is on the part of chromosome 8 (8q24-qter) that is translocated to 2, 14, or 22. Several MYC-related sequences may be pseudogenes. Taub et al. (1982) also mapped the MYC gene to 8q24 and found that in 2 Burkitt cell lines MYC was translocated into a DNA restriction fragment that also encodes the immunoglobulin mu chain gene. In a mouse plasmacytoma, the MYC gene was translocated into the immunoglobulin alpha switch region. Observations such as those of Alitalo et al. (1983) indicate that the same oncogene which in one chromosomal change or rearrangement produces one specific neoplasm results, when altered in a different way, in a different neoplasm. Alitalo et al. (1983) found that the MYC gene, which is involved by translocation in the generation of Burkitt lymphoma, is amplified, resulting in homogeneously staining chromosomal regions (HSRs) in a human neuroendocrine tumor cell line derived from a colon cancer. The HSR resided on a distorted X chromosome; amplification of MYC had been accompanied by translocation of the gene from its normal position on 8q24. Maguire et al. (1983) found that Burkitt and non-Burkitt lymphomas with either an 8;14 or an 8;22 translocation expressed 2- to 5-fold more MYC-specific RNA than B-cell lines without a translocation. Tumor cell lines of American origin with a translocation of either type expressed similar amounts of MYC-specific RNA. Tumor cell lines of African origin contained slightly higher levels of MYC-specific RNA than American lines, but the level did not

correlate with absence or presence of Epstein-Barr virus (EBV). No MOS-related transcripts were found in these tumors. In Burkitt lymphomas bearing the 8;14 translocation, the MYC gene is translocated to a heavy chain switch recombination region (mu or alpha). See Adams et al. (1983). By fluorescence in situ hybridization in combination with R banding, Takahashi et al. (1991) refined the assignment of MYC to 8q24.12-q24.13, distal to fragile site fra(8)(q24.11).

The 14q marker in Burkitt lymphoma was first found by Manolov and Manolova (1972). Zech et al. (1976) showed that the extra chromosomal material joined to the end of one chromosome 14 is derived from the distal part of 8q. Bernheim et al. (1981) found either 2;8 or 8;22 translocation in about 10% of cases. The translocations separate the MYC gene from its normal promoter and 5-prime regulatory machinery, and place it under some regulatory element associated with the immunoglobulin gene. By hybrid cell studies of mouse plasmacytoma cells and Burkitt lymphoma cells, Nishikura et al. (1983) showed that cells containing the MYC gene on a translocation chromosome expressed high levels of human specific MYC transcripts whereas hybrid cells containing the untranslocated MYC gene on the normal chromosome did not contain such MYC mRNA. Usually in t(8;14) translocations, the MYC gene is translocated to 14q. When the break occurs between the MYC first and second exons, both segments are transcriptionally active. Croce et al. (1983) studied somatic cell hybrids between mouse myeloma cells and a Burkitt lymphoma human cell line with a t(8;22) chromosome translocation. The MYC gene was found to remain on chromosome 8q+; the normal chromosome 8 remains transcriptionally silent. The lambda constant region is translocated 3-prime to the MYC oncogene. Yokota et al. (1986) concluded that alterations are found in oncogenes MYC, HRAS, or MYB in more than one-third of human solid tumors. Amplification of MYC was found in advanced widespread tumors and in aggressive primary tumors. Apparent allelic deletions of HRAS and MYB could be correlated with progression and metastasis of carcinomas and sarcomas.

Erikson et al. (1986) studied 2 patients with a t(8;14)(q24;q11) chromosome translocation. In 1, rearrangement was detected in a region immediately 3-prime to the MYC locus. In the second, the breakpoint in the chromosome 14 occurred between genes for the variable and constant regions of the T-cell receptor alpha chain (186880). The constant region locus had translocated to a region more than 38 kb 3-prime to the MYC gene, yet as was shown by the study of hybrids between the human cells and mouse cells, only the hybrids carrying the 8q+ chromosome expressed MYC. Thus, deregulation of the MYC locus can occur not only with translocation of the heavy chain locus or one or the other light chain locus to chromosome 8 but also with translocation of the TCRA locus. The involvement of the MYC oncogene in translocations is the prototype in the relationship between chromosomal abnormalities and oncogenes.

Heim and Mitelman (1987) counted a total of 83 bands that have been found to be specifically involved in primary structural chromosome rearrangements in human cancer. They compared the distribution of these breakpoints with the chromosomal sites of 26 cellular oncogenes which had to that time been mapped to individual bands in the human genome. Nineteen of the 26 oncogenes were located in cancer-associated bands. This clustering is statistically significant ($p = 0.0000012$). They pointed out that cancer may be inflated by errors of karyotype interpretation. Furthermore, it appears that only 1 of the 2 breakpoints in cancer-specific translocations is the site of an oncogene, so that the number of cancer-associated breakpoints that are found to contain oncogenes should theoretically approach 50% of the total. Mitelman (1985) provided a useful catalog of chromosome aberrations in cancer. Duesberg (1987) suggested that cellular cancer genes are not activated oncogenes but rather the result of rare truncations and illegitimate recombinations that alter the germline configuration of cellular genes. See review by Cole (1986). Since MYC is proximal to the thyroglobulin gene (TG; 188450), which is located in the segment 8q24.2-q24.3, MYC may be located in band 8q24.1.

EBV is stably maintained and partially expressed in Burkitt lymphoma and in nasopharyngeal carcinoma. Latently infected cells usually contain multiple episomal copies of nonintegrated viral DNA. In 2 Burkitt cell lines, Henderson et al. (1983) showed that EBV was also integrated into a chromosome, but different chromosomes--nos. 1 and 4. The persistence of EBV in latently infected cells over years of active cell replication may be explained by integration. It is noteworthy that the site of integration is removed from those involved in the translocation. 'The simplest model to explain EBV association with Burkitt tumors is that EBV induces B-cell proliferation and thereby provides enhanced opportunity for chromosomal translocation and malignant degeneration' (Henderson et al., 1983).

Morse et al. (1988) found an MYC rearrangement in a breast carcinoma due to insertion of a LINE-1 (L1) element. (Mobile genetic elements are an important source of genetic variability in both prokaryotes and eukaryotes, including Drosophila, yeast, and mouse. At least 10% of the human genome is composed of repetitive retrotransposon-like sequences including short, interspersed Alu sequences, nonviral retrotransposon-like LINE-1 sequences, and the long terminal repeat (LTR)-containing THE-1 elements. Factor VIII mutations due to L1 insertions have been reported (306700) and an Alu transposition event has been found in human lung carcinoma cells (Lin et al., 1988). The RTVL-H family of human endogenous retrovirus-like elements has approximately 1,000 intact members and a similar number of solitary LTRs in the haploid genome. The intact RTVL-H sequences are 5.8 kb long, have 5-prime and 3-prime LTRs and have some segments of sequence similarity to mammalian retroviruses in the putative gag and pol regions. Mager and Goodchild (1989) demonstrated DNA variation in 2 sibs representing a deletion due to homologous recombination between the 5-prime and 3-prime LTRs of a RTVL-H sequence.) Specific types of human papillomavirus (HPV), mostly HPV type 16 (HPV16) and type 18 (HPV18), are associated with genital carcinomas such as those of the cervix and their noninvasive precursors (167959, 167960). In intraepithelial neoplasia, HPV DNA is detected most commonly as episomal molecules, whereas it is found integrated in the cell genome in the majority of invasive carcinomas. By chromosomal in situ hybridization experiments, Couturier et al. (1991) determined the localization of integrated HPV16 or HPV18 genomes in genital cancers. In 3 cancers, HPV sequences were located in band 8q24.1, which contains the MYC gene, and in 1 cancer, HPV sequences were located in band 2p24, which contains the NMYC gene (164840). In 3 of the 4 cases, the protooncogene located near integrated viral sequences was found to be structurally altered and/or overexpressed.

Atchley and Fitch (1995) described phylogenetic analyses for 45 MYC protein sequences. A gene duplication early in vertebrate evolution produced the c-myc lineage and another lineage that later gave rise to the N- and L-myc lineages by another gene duplication. Evolutionary divergence in the MYC gene family corresponded closely to the known branching order of the major vertebrate groups. The closely related dimerization partner protein MAX (154950) exhibited significantly less variability than MYC. Atchley and Fitch (1995) suggested a reduced variability in MAX stems from natural selection acting to preserve dimerization capability with products of MYC and related genes.

Cell proliferation is regulated by the induction of growth promoting genes and the suppression of growth inhibitory genes. Malignant growth can result from the altered balance of expression of these genes in favor of cell proliferation. Induction of the transcription factor MYC promotes cell proliferation and transformation by activating growth-promoting genes, including the ornithine decarboxylase (ODC1; 165640) and CDC25A (116947) genes. Lee et al. (1997) showed that MYC transcriptionally represses the expression of the growth arrest gene (GAS1; 139185). A conserved MYC structure, MYC box 2, is required for repression of GAS1 and for MYC induction of proliferation and transformation, but not for activation of ODC1.

The MYC protein activates transcription as part of a heteromeric complex with MAX. However, cells

transformed by MYC are characterized by the loss of expression of numerous genes, suggesting that MYC may also repress gene expression. By searching for proteins that may mediate gene repression by MYC, Peukert et al. (1997) identified ZNF151 (604084), which they called MIZ1 for 'MYC-interacting zinc finger protein-1.' MIZ1 interacts specifically with the helix-loop-helix domain of MYC and NMYC. The predicted MIZ1 protein contains a POZ (poxvirus and zinc finger) domain, which appears to act as a negative regulatory domain for transcription factor function, and 13 zinc finger domains. MIZ1 has a potent growth arrest function and can bind to and transactivate the adenovirus major late and cyclin D1 (CCND1; 168461) promoters. Interaction between MIZ1 and MYC overcomes MIZ1-induced growth arrest, inhibits MIZ1 transactivation, induces MIZ1 nuclear sequestration, and renders MIZ1 insoluble in vivo. These effects depend on the integrity of the POZ domain of MIZ1. Peukert et al. (1997) suggested that MYC inhibits gene transcription by activating the latent inhibitory functions of the MIZ1 POZ domain.

Grandori et al. (1996) identified DDX18 (606355) as a direct in vivo target of Myc and Max and hypothesized that Myc may exert its effects on cell behavior through proteins that affect RNA structure and metabolism.

He et al. (1998) provided a molecular framework for understanding the previously enigmatic overexpression of MYC in colorectal cancers. Inactivating mutations in the adenomatous polyposis coli gene (APC; 175100), found in most colorectal cancers, cause aberrant accumulation of beta-catenin (CTNNB1; 116806), which then binds T-cell factor 4 (TCF4; 602228), causing increased transcriptional activation of unknown genes. He et al. (1998) showed that the MYC oncogene is a target in this signaling pathway. They showed that expression of MYC is repressed by wildtype APC and activated by beta-catenin, and that effects are mediated through TCF4 binding sites in the MYC promoter.

Wu et al. (1999) demonstrated that the MYC protein represses the expression of ferritin-H (134770), which sequesters intracellular iron, and stimulates the expression of iron regulatory protein-2 (IRP2; 147582), which increases the intracellular iron pool. Downregulation of ferritin-H expression was required for cell transformation by c-myc. Wu et al. (1999) further demonstrated that the downregulation of ferritin-H expression was independent of c-myc-induced changes in cell cycle activity. The authors concluded that this function for c-myc is consistent with observations that iron chelation leads to growth arrest.

Contrary to the previous belief that MYC is wildtype in both types of tumors, Bhatia et al. (1993) found that 65% of 57 Burkitt lymphomas and 30% of 10 mouse plasmacytomas exhibited at least 1 amino acid substitution. These mutations were apparently homozygous in all Burkitt lymphoma cell lines tested and in 2 tumor biopsies, implying that the mutations often occur before MYC/IG translocation. In the mouse plasmacytomas, only the mutant myc allele was expressed, indicating a functional homozygosity with occurrence of mutations at the translocation. Many of the observed mutations were clustered in regions associated with transcriptional activation and apoptosis, and in the Burkitt lymphomas, they frequently occurred at sites of phosphorylation, suggesting that the mutations had a pathogenetic role. Most of the mutations observed were clearly not polymorphisms, for reasons in addition to the large number of different mutations observed: 1) a high proportion were missense mutations; 2) most tumors contained multiple mutations; and 3) each tumor had a unique pattern of mutations.

Wu et al. (1999) demonstrated direct activation of telomerase by MYC. Telomerase is the ribonuclear protein complex expressed in proliferating and transformed cells, in which it preserves chromosomal integrity by maintaining telomere length. MYC activates telomerase by inducing expression of its catalytic subunit, telomerase-reverse transcriptase (TERT; 187270). Telomerase complex activity is dependent on TERT, a specialized type of reverse transcriptase. Wu et al. (1999) showed that TERT is a

target of MYC activity and identified a pathway linking cell proliferation and chromosome integrity in normal and neoplastic cells.

Wang et al. (2000) demonstrated that TERT-driven cell proliferation is not genoprotective because it is associated with activation of the MYC oncogene. Human mammary epithelial cells, which normally stop dividing in culture at 55 to 60 population doublings (PDs), were infected with human TERT retrovirus at PD40 and maintained until PD250. Wang et al. (2000) then tested whether telomerase activity was essential for the immortalized phenotype by excising the TERT retrovirus at PD150 using Cre recombinase. The resulting cells were maintained for at least another 20 population doublings, and no decline in growth rates in either pooled cells or individual clones was observed. Ectopic expression of MYC was found to be upregulated between 107 and 135 population doublings. Wang et al. (2000) suggested that under standard culture conditions, extension of lifespan by telomerase selects for MYC overexpression in human mammary epithelial cells.

MYC induces transcription of the E2F1 (189971), E2F2 (600426), and E2F3 (600427) genes. Using primary mouse embryo fibroblasts deleted for individual E2f genes, Leone et al. (2001) showed that MYC-induced S phase and apoptosis requires distinct E2F activities. The ability of Myc to induce S phase was impaired in the absence of either E2f2 or E2f3 but not E2f1 or E2f4 (600659). In contrast, the ability of Myc to induce apoptosis was markedly reduced in cells deleted for E2f1 but not E2f2 or E2f3. The authors proposed that the induction of specific E2F activities is an essential component in the MYC pathways that control cell proliferation and cell fate decisions.

In addition to immunoglobulin V genes, the 5-prime sequences of BCL6 (109565) and FAS (TNFRSF6; 134637) are mutated in normal germinal center B lymphocytes. Genomic instability promotes tumorigenesis through defective chromosome segregation and DNA mismatch repair inactivation. By screening 18 loci for mutations, Pasqualucci et al. (2001) identified changes in the germline sequences of PIM1 (164960), MYC, ARHH (602037), and/or PAX5 (167414), in addition to BCL6, in a majority of diffuse large-cell lymphomas (DLCLs; see 601889). No mutations in PIM1, MYC, ARHH, and PAX5 were detected in germinal-center lymphocytes, naive B cells, or B-cell malignancies other than DLCLs. MYC mutations, which were found in 32% of DLCLs, were located downstream of the major P1/P2 promoters in exon 1 or downstream of the minor P3 promoter in exon 2. FISH analysis indicated that hypermutation in these genes is not due to chromosomal translocation, as seen in Burkitt lymphoma (113970). Chromosomal translocation, however, may be an outcome of hypermutation. Specific features of the hypermutation process, including the predominance of single nucleotide substitutions with occasional deletions or duplications, a preference for transitions over transversions, and a specific motif targeting RGYW, were recognizable in each of the hypermutated loci. Pasqualucci et al. (2001) proposed that aberrant hypermutation of regulatory and coding sequences of genes that do not represent physiologic targets may provide the basis for DLCL pathogenesis and explain its phenotypic and clinical heterogeneity. This hypermutation malfunction is unlikely to be due to defective DNA mismatch repair and does not appear to involve activation-induced deaminase (AICDA; 605257)

Trumpp et al. (2001) reported the generation of an allelic series of mice in which Myc expression is incrementally reduced to zero. Fibroblasts from these mice showed reduced proliferation, and after complete loss of Myc function they exited the cell cycle. Trumpp et al. (2001) showed that Myc activity is not needed for cellular growth but does determine the percentage of activated T cells that reenter the cell cycle. In vivo, reduction of Myc levels resulted in reduced body mass owing to multiorgan hypoplasia, in contrast to Drosophila dmyc mutants, which are smaller as a result of hypotrophy. Trumpp et al. (2001) found that dmyc substitutes for Myc in fibroblasts, indicating they have similar biologic activities. Trumpp et al. (2001) concluded that there may be fundamental differences in the mechanisms by which mammals and insects control body size, and proposed that in mammals MYC

controls the decision to divide or not to divide and thereby functions as a crucial mediator of signals that determine organ and body size.

Feng et al. (2002) showed that MYC physically interacts with SMAD2 (601366) and SMAD3 (603109), 2 specific signal transducers involved in TGF-beta (190180) signaling. Through its direct interaction with SMADs, MYC binds to the SP1 (189906)-SMAD complex on the promoter of the p15(INK4B) gene (600431), thereby inhibiting the TGF-beta-induced transcriptional activity of SP1 and SMAD/SP1-dependent transcription of the p15(INK4B) gene. The oncogenic MYC promotes cell growth and cancer development partly by inhibiting the growth inhibitory functions of SMADs.

To explore the role of MYC in carcinogenesis, Pelengaris et al. (2002) developed a reversible transgenic mouse model of pancreatic beta-cell oncogenesis using a switchable form of the MYC protein. Activation of MYC in adult, mature beta cells induced uniform beta-cell proliferation but was accompanied by overwhelming apoptosis that rapidly eroded beta-cell mass. Thus, the oncogenic potential of MYC in beta cells was masked by apoptosis. Upon suppression of MYC-induced beta-cell apoptosis by coexpression of BCLXL (600039), MYC triggered rapid and uniform progression into angiogenic, invasive tumors. Subsequent MYC deactivation induced rapid regression associated with vascular degeneration and beta-cell apoptosis. These data indicated that highly complex neoplastic lesions can be both induced and maintained in vivo by a simple combination of 2 interlocking molecular lesions.

Jain et al. (2002) used a conditional transgenic mouse model for MYC-induced tumorigenesis to demonstrate that brief inactivation of MYC results in the sustained regression of tumors and the differentiation of osteogenic sarcoma cells into mature osteocytes. Subsequent reactivation of MYC did not restore the cells' malignant properties but instead induced apoptosis. Thus, Jain et al. (2002) concluded that brief MYC inactivation appears to cause epigenetic changes in tumor cells that render them insensitive to MYC-induced tumorigenesis. The authors raised the possibility that transient inactivation of MYC may be an effective therapy for certain cancers.

To identify target genes of MYC, Menssen and Hermeking (2002) performed serial analysis of gene expression (SAGE) after adenoviral expression of MYC in primary human umbilical vein endothelial cells. Induction of 53 genes was confirmed using microarray analysis and quanitative real-time PCR. Among these genes was MetAP2, also called p67 (601870), which encodes an activator of translational initiation and represents a validated target for inhibition of neovascularization. Furthermore, MYC induced 3 cell cycle regulatory genes and 3 DNA repair genes, suggesting that MYC couples DNA replication to processes preserving the integrity of the genome. MNT (603039), a MAX-binding antagonist of MYC function, was upregulated, implying a negative feedback loop. In vivo promoter occupancy by MYC was detected by chromatin immunoprecipitation for at least 5 genes, showing that they are direct MYC targets. The authors suggested that the MYC-regulated genes identified by this study define a set of bonafide MYC targets and may have potential therapeutic value for inhibition of cancer cell proliferation, tumor vascularization, and restenosis.

Leven (2002) discussed and diagrammed the complex web of MYC-related pathways involved in growth, proliferation, and apoptosis.

Vafa et al. (2002) showed that brief MYC activation can induce DNA damage prior to S phase in normal human fibroblasts. Damage correlated with induction of reactive oxygen species (ROS) without induction of apoptosis. Deregulated MYC partially disabled the p53-mediated DNA damage response, enabling cells with damaged genomes to enter the cycle, resulting in poor clonogenic survival. An

antioxidant reduced ROS, decreased DNA damage and p53 activation, and improved survival. The authors proposed that oncogene activation can induce DNA damage and override damage controls, thereby accelerating tumor progression via genetic instability.

ALLELIC VARIANTS
(selected examples)

.0001 BURKITT LYMPHOMA [MYC, PRO57SER]

Bhatia et al. (1993) found homozygosity for a CCC-to-TCC transition converting proline-57 to serine in Burkitt lymphoma-20 (DIF).

.0002 BURKITT LYMPHOMA [MYC, ASN86THR]

Bhatia et al. (1993) found homozygosity for an AAC-to-ACC transition converting asparagine-86 to threonine in Burkitt lymphoma-21 (DS179).

.0003 BURKITT LYMPHOMA [MYC, GLU39ASP]

Bhatia et al. (1993) found homozygosity for a GAG-to-GAC transversion converting glutamic acid-39 to to aspartic acid in Burkitt lymphoma-25 (JLP).

.0004 BURKITT LYMPHOMA [MYC, PRO59ALA]

Bhatia et al. (1993) found homozygosity for a CCG to GCG transversion converting proline-59 to alanine in Burkitt lymphoma-30 (WMN).

SEE ALSO

Battey et al. (1983); Beimling et al. (1985); Bernard et al. (1983); Colby et al. (1983); Dalla-Favera et al. (1982); Dunnick et al. (1983); Erikson et al. (1983); Hamlyn and Rabbitts (1983); Hayday et al. (1984); Magrath et al. (1983); Marcu et al. (1983); Murphy et al. (1986); Neel et al. (1982); Persson et al. (1984); Peschle et al. (1984); Saito et al. (1983); Sakaguchi et al. (1983); Watt et al. (1983); Watt et al. (1983)

REFERENCES

1. Adams, J. M.; Gerondakis, S.; Webb, E.; Corcoran, L. M.; Cory, S. :
Cellular myc oncogene is altered by chromosome translocation to an immunoglobulin locus in murine plasmacytomas and is rearranged similarly in human Burkitt lymphomas. *Proc. Nat. Acad. Sci.* 80: 1982-1986, 1983.
PubMed ID : 6572957

2. Alitalo, K.; Schwab, M.; Lin, C. C.; Varmus, H. E.; Bishop, J. M. :
Homogeneously staining chromosomal regions contain amplified copies of an abundantly expressed cellular oncogene (c-myc) in malignant neuroendocrine cells from a human colon carcinoma. *Proc. Nat. Acad. Sci.* 80: 1707-1711, 1983.
PubMed ID : 6300869

3. Atchley, W. R.; Fitch, W. M. :
Myc and Max: molecular evolution of a family of proto-oncogene products and their dimerization partner. *Proc. Nat. Acad. Sci.* 92: 10217-10221, 1995.
PubMed ID : 7479755

4. Battey, J.; Moulding, C.; Taub, R.; Murphy, W.; Stewart, T.; Potter, H.; Lenoir, G.; Leder, P. :
The human c-myc oncogene: structural consequences of translocation into the IgH locus in Burkitt lymphoma. *Cell* 34: 779-787, 1983.
PubMed ID : 6414718

5. Beimling, P.; Benter, T.; Sander, T.; Moelling, K. :
Isolation and characterization of the human cellular myc gene product. *Biochemistry* 24: 6349-6355, 1985.
PubMed ID : 3002438

6. Bernard, O.; Cory, S.; Gerondakis, S.; Webb, E.; Adams, J. M. :
Sequence of the murine and human cellular myc oncogenes and two modes of myc transcription resulting from chromosome translocation in B lymphoid tumours. *EMBO J.* 2: 2375-2383, 1983.
PubMed ID : 6321164

7. Bernheim, A.; Berger, R.; Lenoir, G. :
Cytogenetic studies on African Burkitt's lymphoma cell lines: t(8;14), t(2;8) and t(8;22) translocations. *Cancer Genet. Cytogenet.* 3: 307-315, 1981.
PubMed ID : 7260888

8. Bhatia, K.; Huppi, K.; Spangler, G.; Siwarski, D.; Iyer, R.; Magrath, I. :
Point mutations in the c-Myc transactivation domain are common in Burkitt's lymphoma and mouse plasmacytomas. *Nature Genet.* 5: 56-61, 1993.
PubMed ID : 8220424

9. Colby, W. W.; Chen, E. Y.; Smith, D. H.; Levinson, A. D. :
Identification and nucleotide sequence of a human locus homologous to the v-myc oncogene of avian myelocytomatosis virus MC29. *Nature* 301: 722-725, 1983.
PubMed ID : 6298632

10. Cole, M. D. :
The myc oncogene: its role in transformation and differentiation. *Annu. Rev. Genet.* 20: 361-384, 1986.
PubMed ID : 3028245

11. Collins, S.; Groudine, M. :
Amplification of endogenous myc-related DNA sequences in a human myeloid leukaemia cell line. *Nature* 298: 679-681, 1982.
PubMed ID : 6285209

12. Couturier, J.; Sastre-Garau, X.; Schneider-Maunoury, S.; Labib, A.; Orth, G. :
Integration of papillomavirus DNA near myc genes in genital carcinomas and its consequences for proto-oncogene expression. *J. Virol.* 65: 4534-4538, 1991.
PubMed ID : 1649348

13. Croce, C. M.; Thierfelder, W.; Erikson, J.; Nishikura, K.; Finan, J.; Lenoir, G. M.; Nowell, P. C. :
Transcriptional activation of an unrearranged and untranslocated c-myc oncogene by translocation of a C-lambda locus in Burkitt lymphoma cells. *Proc. Nat. Acad. Sci.* 80: 6922-6926, 1983.
PubMed ID : 6417658

14. Dalla-Favera, R.; Bregni, M.; Erikson, J.; Patterson, D.; Gallo, R. C.; Croce, C. M. :
Human c-myc onc gene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells. *Proc. Nat. Acad. Sci.* 79: 7824-7827, 1982.
PubMed ID : 6961453

15. Dalla-Favera, R.; Gelmann, E. P.; Martinotti, S.; Franchini, G.; Papas, T. S.; Gallo, R. C.; Wong-Staal, F. :
Cloning and characterization of different human sequences related to the onc gene (v-myc) of avian myelocytomatosis virus (MC29). *Proc. Nat. Acad. Sci.* 79: 6497-6501, 1982.
PubMed ID : 6292905

16. Duesberg, P. H. :
Cancer genes: rare recombinants instead of activated oncogenes (a review). *Proc. Nat. Acad. Sci.* 84: 2117-2124, 1987.
PubMed ID : 3550807

17. Dunnick, W.; Shell, B. E.; Dery, C. :
DNA sequences near the site of reciprocal recombination between a c-myc oncogene and an immunoglobulin switch region. *Proc. Nat. Acad. Sci.* 80: 7269-7273, 1983.
PubMed ID : 6316351

18. Erikson, J.; Finger, L.; Sun, L.; ar-Rushdi, A.; Nishikura, K.; Minowada, J.; Finan, J.; Emanuel, B. S.; Nowell, P. C.; Croce, C. M. :
Deregulation of c-myc by translocation of the alpha-locus of the T-cell receptor in T-cell leukemias. *Science* 232: 884-886, 1986.
PubMed ID : 3486470

19. Erikson, J.; Nishikura, K.; ar-Rushdi, A.; Finan, J.; Emanuel, B.; Lenoir, G.; Nowell, P. C.; Croce, C. M. :
Translocation of an immunoglobulin kappa locus to a region 3-prime of an unrearranged c-myc oncogene enhances c-myc transcription. *Proc. Nat. Acad. Sci.* 80: 7581-7585, 1983.
PubMed ID : 6424112

20. Feng, X.-H.; Liang, Y.-Y.; Liang, M.; Zhai, W.; Lin, X. :
Direct interaction of c-Myc with Smad2 and Smad3 to inhibit TGF-beta-mediated induction of the CDK inhibitor p15(Ink4B). *Molec. Cell* 9: 133-143, 2002.
PubMed ID : 11804592

21. Grandori, C.; Mac, J.; Siebelt, F.; Ayer, D. E.; Eisenman, R. N. :
Myc-Max heterodimers activate a DEAD box gene and interact with multiple E box-related sites in vivo. *EMBO J.* 15: 4344-4357, 1996.
PubMed ID : 8861962

22. Hamlyn, P. H.; Rabbitts, T. H. :

Translocation joins c-myc and immunoglobulin gamma-1 genes in a Burkitt lymphoma revealing a third exon in the c-myc oncogene. *Nature* 304: 135-139, 1983.
PubMed ID : 6306472

23. Hayday, A. C.; Gillies, S. D.; Saito, H.; Wood, C.; Wiman, K.; Hayward, W. S.; Tonegawa, S. :
Activation of a translocated human c-myc gene by an enhancer in the immunoglobulin heavy-chain locus. *Nature* 307: 334-340, 1984.
PubMed ID : 6420706

24. He, T.-C.; Sparks, A. B.; Rago, C.; Hermeking, H.; Zawel, L.; da Costa, L. T.; Morin, P. J.; Vogelstein, B.; Kinzler, K. W. :
Identification of c-MYC as a target of the APC pathway. *Science* 281: 1509-1512, 1998.
PubMed ID : 9727977

25. Heim, S.; Mitelman, F. :
Nineteen of 26 cellular oncogenes precisely localized in the human genome map to one of the 83 bands involved in primary cancer-specific rearrangements. *Hum. Genet.* 75: 70-72, 1987.
PubMed ID : 3468057

26. Henderson, A.; Ripley, S.; Heller, M.; Kieff, E. :
Chromosome site for Epstein-Barr virus DNA in a Burkitt tumor cell line and in lymphocytes growth-transformed in vitro. *Proc. Nat. Acad. Sci.* 80: 1987-1991, 1983.
PubMed ID : 6300885

27. Jain, M.; Arvanitis, C.; Chu, K.; Dewey, W.; Leonhardt, E.; Trinh, M.; Sundberg, C. D.; Bishop, J. M.; Felsher, D. W. :
Sustained loss of a neoplastic phenotype by brief inactivation of MYC. *Science* 297: 102-104, 2002.
PubMed ID : 12098700

28. Leder, P. :
Personal Communication. Boston, Mass., 10/1/1982.

29. Lee, T. C.; Li, L.; Philipson, L.; Ziff, E. B. :
Myc represses transcription of the growth arrest gene gas1. *Proc. Nat. Acad. Sci.* 94: 12886-12891, 1997.
PubMed ID : 9371770

30. Leone, G.; Sears, R.; Huang, E.; Rempel, R.; Nuckolls, F.; Park, C.-H.; Giangrande, P.; Wu, L.; Saavedra, H. I.; Field, S. J.; Thompson, M. A.; Yang, H.; Fujiwara, Y.; Greenberg, M. E.; Orkin, S.; Smith, C.; Nevins, J. R. :
Myc requires distinct E2F activities to induce S phase and apoptosis. *Molec. Cell* 8: 105-113, 2001.
PubMed ID : 11511364

31. Leven, D. :
Disentangling the MYC web. (Commentary) *Proc. Nat. Acad. Sci.* 99: 5757-5759, 2002.
PubMed ID : 11983876

32. Lin, C. S.; Goldthwait, D. A.; Samols, D. :

Identification of Alu transposition in human lung carcinoma cells. *Cell* 54: 153-159, 1988.
PubMed ID : 2839298

33. Mager, D. L.; Goodchild, N. L. :
Homologous recombination between the LTRs of a human retrovirus-like element causes a 5-kb deletion in two siblings. *Am. J. Hum. Genet.* 45: 848-854, 1989.
PubMed ID : 2573998

34. Magrath, I.; Erikson, J.; Whang-Peng, J.; Sieverts, H.; Armstrong, G.; Benjamin, D.; Triche, T.; Alabaster, O.; Croce, C. M. :
Synthesis of kappa light chains by cell lines containing an 8;22 chromosomal translocation derived from a male homosexual with Burkitt's lymphoma. *Science* 222: 1094-1098, 1983.
PubMed ID : 6316501

35. Maguire, R. T.; Robins, T. S.; Thorgeirsson, S. S.; Heilman, C. A. :
Expression of cellular myc and mos genes in undifferentiated B cell lymphomas of Burkitt and non-Burkitt types. *Proc. Nat. Acad. Sci.* 80: 1947-1950, 1983.
PubMed ID : 6300881

36. Manolov, G.; Manolova, Y. :
Marker band in one chromosome 14 from Burkitt lymphomas. *Nature* 237: 33-34, 1972.
PubMed ID : 4113130

37. Marcu, K. B.; Harris, L. J.; Stanton, L. W.; Erikson, J.; Watt, R.; Croce, C. M. :
Transcriptionally active c-myc oncogene is contained within NIARD, a DNA sequence associated with chromosome translocations in B-cell neoplasia. *Proc. Nat. Acad. Sci.* 80: 519-523, 1983.
PubMed ID : 6188153

38. Menssen, A.; Hermeking, H. :
Characterization of the c-MYC-regulated transcriptome by SAGE: identification and analysis of c-MYC target genes. *Proc. Nat. Acad. Sci.* 99: 6274-6279, 2002.
PubMed ID : 11983916

39. Mitelman, F. :
Catalog of Chromosome Aberrations in Cancer. New York: Alan R. Liss (pub.) (2nd ed.) 1985.

40. Morse, B.; Rotherg, P. G.; South, V. J.; Spandorfer, J. M.; Astrin, S. M. :
Insertional mutagenesis of the myc locus by a LINE-1 sequence in a human breast carcinoma. *Nature* 333: 87-90, 1988.
PubMed ID : 2834650

41. Murphy, W.; Sarid, J.; Taub, R.; Vasicek, T.; Battey, J.; Lenoir, G.; Leder, P. :
A translocated human c-myc oncogene is altered in a conserved coding sequence. *Proc. Nat. Acad. Sci.* 83: 2939-2943, 1986.
PubMed ID : 3517879

42. Neel, B. G.; Jhanwar, S. C.; Chaganti, R. S. K.; Hayward, W. S. :
Two human c-onc genes are located on the long arm of chromosome 8. *Proc. Nat. Acad. Sci.*

79: 7842-7846, 1982.
PubMed ID : 6961456

43. Nishikura, K.; ar-Rushdi, A.; Erikson, J.; Watt, R.; Rovera, G.; Croce, C. M. :
Differential expression of the normal and of the translocated human c-myc oncogenes in B cells. *Proc. Nat. Acad. Sci.* 80: 4822-4826, 1983.
PubMed ID : 6308654

44. Pasqualucci, L.; Neumeister, P.; Goossens, T.; Nanjangud, G.; Chaganti, R. S. K.; Kuppers, R.; Dalla-Favera, R. :
Hypermutation of multiple proto-oncogenes in B-cell diffuse large-cell lymphomas. *Nature* 412: 341-346, 2001.
PubMed ID : 11460166

45. Pelengaris, S.; Khan, M.; Evan, G. I. :
Suppression of Myc-induced apoptosis in beta cells exposes multiple oncogenic properties of Myc and triggers carcinogenic progression. *Cell* 109: 321-334, 2002.
PubMed ID : 12015982

46. Persson, H.; Hennighausen, L.; Taub, R.; DeGrado, W.; Leder, P. :
Antibodies to human c-myc oncogene product: evidence of an evolutionarily conserved protein induced during cell proliferation. *Science* 225: 687-693, 1984.
PubMed ID : 6431612

47. Persson, H.; Leder, P. :
Nuclear localization and DNA binding properties of a protein expressed by human c-myc oncogene. *Science* 225: 718-721, 1984.
PubMed ID : 6463648

48. Peschle, C.; Mavilio, F.; Sposi, N. M.; Giampaolo, A.; Care, A.; Bottero, L.; Bruno, M.; Mastroberardino, G.; Gastaldi, R.; Testa, M. G.; Alimena, G.; Amadori, S.; Mandelli, F. :
Translocation and rearrangement of c-myc into immunoglobulin alpha heavy chain locus in primary cells from acute lymphocytic leukemia. *Proc. Nat. Acad. Sci.* 81: 5514-5518, 1984.
PubMed ID : 6089208

49. Peukert, K.; Staller, P.; Schneider, A.; Carmichael, G.; Hanel, F.; Eilers, M. :
An alternative pathway for gene regulation by Myc. *EMBO J.* 16: 5672-5686, 1997.
PubMed ID : 9312026

50. Saito, H.; Hayday, A. C.; Wiman, K.; Hayward, W. S.; Tonegawa, S. :
Activation of the c-myc gene by translocation: a model for translational control. *Proc. Nat. Acad. Sci.* 80: 7476-7480, 1983.
PubMed ID : 6324175

51. Sakaguchi, A. Y.; Lalley, P. A.; Naylor, S. L. :
Human and mouse cellular myc protooncogenes reside on chromosomes involved in numerical and structural aberrations in cancer. *Somat. Cell Genet.* 9: 391-405, 1983.
PubMed ID : 6857448

52. Shilo, B. Z.; Weinberg, R. A. :

DNA sequences homologous to vertebrate oncogenes are conserved in Drosophila melanogaster. *Proc. Nat. Acad. Sci.* 78: 6789-6792, 1981.
PubMed ID : 6796966

53. Takahashi, E.; Hori, T.; O'Connell, P.; Leppert, M.; White, R. :
Mapping of the MYC gene to band 8q24.12-q24.13 by R-banding and distal to fra(8) (q24.11), FRA8E, by fluorescence in situ hybridization. *Cytogenet. Cell Genet.* 57: 109-111, 1991.
PubMed ID : 1914517

54. Taub, R.; Kirsch, I.; Morton, C.; Lenoir, G.; Swan, D.; Tronick, S.; Aaronson, S.; Leder, P. :
Translocation of the c-myc gene into the immunoglobulin heavy chain locus in human Burkitt lymphoma and murine plasmacytoma cells. *Proc. Nat. Acad. Sci.* 79: 7837-7841, 1982.

PubMed ID : 6818551

55. Trumpp, A.; Refaeli, Y.; Oskarsson, T.; Gasser, S.; Murphy, M.; Martin, G. R.; Bishop, J. M. :
c-Myc regulates mammalian body size by controlling cell number but not cell size. *Nature* 414: 768-773, 2001.
PubMed ID : 11742404

56. Vafa, O.; Wade, M.; Kern, S.; Beeche, M.; Pandita, T. K.; Hampton, G. M.; Wahl, G. M. :
c-Myc can induce DNA damage, increase reactive oxygen species, and mitigate p53 function: a mechanism for oncogene-induced genetic instability. *Molec. Cell* 9: 1031-1044, 2002.
PubMed ID : 12049739

57. Wang, J.; Hannon, G. J.; Beach, D. H. :
Risky immortalization by telomerase. (Letter) *Nature* 405: 755-756, 2000.
PubMed ID : 10866187

58. Watt, R.; Nishikura, K.; Sorrentino, J.; ar-Rushdi, A.; Croce, C. M.; Rovera, G. :
The structure and nucleotide sequence of the 5-prime end of the human c-myc oncogene. *Proc. Nat. Acad. Sci.* 80: 6307-6311, 1983.
PubMed ID : 6578511

59. Watt, R.; Stanton, L. W.; Marcu, K. B.; Gallo, R. C.; Croce, C. M.; Rovera, G. :
Nucleotide sequence of cloned cDNA of human c-myc oncogene. *Nature* 303: 725-728, 1983.
PubMed ID : 6304538

60. Wu, K.-J.; Grandori, C.; Amacker, M.; Simon-Vermot, N.; Polack, A.; Lingner, J.; Dalla-Favera, R. :
Direct activation of TERT transcription by c-MYC. *Nature Genet.* 21: 220-224, 1999.
PubMed ID : 9988278

61. Wu, K.-J.; Polack, A.; Dalla-Favera, R. :
Coordinated regulation of iron-controlling genes, H-ferritin and IRP2, by c-MYC. *Science* 283: 676-679, 1999.
PubMed ID : 9924025

62. Yokota, J.; Tsunetsugu-Yokota, Y.; Battifora, H.; Le Fevre, C.; Cline, M. J. :

Alterations of myc, myb, and ras(Ha) proto-oncogenes in cancers are frequent and show clinical correlation. *Science* 231: 261-265, 1986.
PubMed ID : 3941898

63. Zech, L.; Haglund, U.; Nilsson, K.; Klein, G. :
Characteristic chromosomal abnormalities in biopsies and lymphoid-cell lines from patients with Burkitt and non-Burkitt lymphomas. *Int. J. Cancer* 17: 47-56, 1976.
PubMed ID : 946170

CONTRIBUTORS

Stylianos E. Antonarakis - updated : 9/18/2002
Ada Hamosh - updated : 7/24/2002
Victor A. McKusick - updated : 6/6/2002
Stylianos E. Antonarakis - updated : 5/13/2002
Stylianos E. Antonarakis - updated : 1/30/2002
Ada Hamosh - updated : 12/18/2001
Dawn Watkins-Chow - updated : 10/4/2001
Paul J. Converse - updated : 8/7/2001
Stylianos E. Antonarakis - updated : 8/3/2001
Ada Hamosh - updated : 6/14/2000
Patti M. Sherman - updated : 8/31/1999
Ada Hamosh - updated : 1/29/1999
Victor A. McKusick - updated : 1/29/1999
Victor A. McKusick - updated : 9/2/1998
Victor A. McKusick - updated : 2/24/1998

CREATION DATE

Victor A. McKusick : 6/23/1986

EDIT HISTORY

mgross : 9/18/2002
cwells : 7/26/2002
terry : 7/24/2002
mgross : 6/11/2002
terry : 6/6/2002
mgross : 5/13/2002
mgross : 1/30/2002
alopez : 1/2/2002
terry : 12/18/2001
carol : 10/4/2001
mgross : 8/7/2001
mgross : 8/7/2001
mgross : 8/3/2001
alopez : 6/14/2000
mgross : 9/1/1999
psherman : 8/31/1999
alopez : 2/1/1999

- alopez : 2/1/1999
  alopez : 1/29/1999
  terry : 1/29/1999
  dkim : 12/15/1998
  alopez : 9/3/1998
  terry : 9/2/1998
  psherman : 4/15/1998
  alopez : 2/25/1998
  terry : 2/24/1998
  mark : 11/10/1995
  mimadm : 6/7/1995
  davew : 7/28/1994
  warfield : 4/14/1994
  carol : 9/9/1993
  carol : 6/25/1993

Display | Detailed | Save | Text | Clip Add